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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,637	02/06/2007	Dieter Scheller	6102-000034/US/NP	2828

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,637	SCHELLER ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-21* is/are pending in the application.

4a) Of the above claim(s) *15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-14 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 01/13/2009 were entered.

Response to Arguments

2. Applicants' arguments, filed 01/13/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

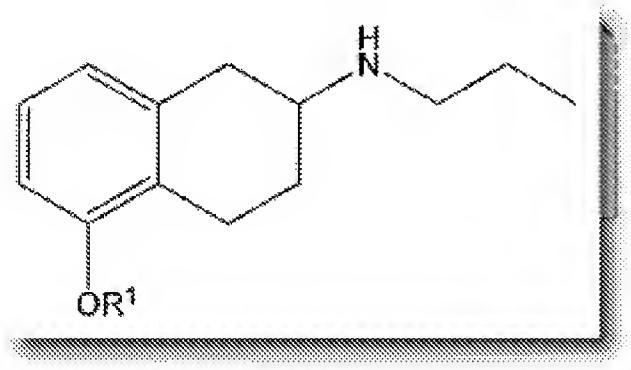
3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. **Claims 10-12, 14 and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Hacksell et al* (cited in a previous Action) in view of *Wikstrom et al* (cited in a previous Action) and *Rodenhuis* (cited in a previous Action).**

6. As amended, instant claim 19 is drawn to a compound having the formula



in the (S)-configuration that, when administered to a human body, are cleaved, processed or metabolized to (S)-2-N-propylamino-5-hydroxytetralin.

7. As discussed in the previous Action, *Hacksell et al* clearly teach that racemic 2-N-propylamino-5-hydroxytetralin is a potent dopamine agonist (Page 1472, Table I, compound 8). Although Applicant states that "aminotetralins with N,N-dialkylation were the most active and appropriate compounds for the intended oral administration" (Applicant's Specification, Page 2, Paragraph 0008) it is still the case that racemic 2-N-propylamino-5-hydroxytetralin demonstrates significant agonistic activity. In fact, racemic 2-N-propylamino-5-hydroxytetralin is significantly more potent that apomorphine (Pages 1472-1473, Table I, compare compounds 8 and apomorphine). Accordingly, one of ordinary skill in the art would have been motivated to formulate compounds and compositions containing 2-N-propylamino-5-hydroxytetralin.

8. Applicant, however, argues that the skilled artisan would not have been motivated to formulate compounds and compositions containing 2-N-propylamino-5-hydroxytetralin. Applicant points to *Swart et al* (Toxicol Meth 3:279-290, 1993) which state that 2-N-propylamino-5-hydroxytetralin showed weak affinity in dopaminergic receptor binding studies (Page 289). However, this conclusion was based on the ability of 2-N-propylamino-5-hydroxytetralin to displace ^{3}H-N-0437 (Page 286). Accordingly, while *Swart et al* indicate that 2-N-propylamino-5-hydroxytetralin does not bind dopaminergic receptors as efficiently as N-0437, *Swart et al* do not overcome the data of *Hacksell et al* which clearly demonstrate that 2-N-propylamino-5-hydroxytetralin possesses significant dopamine agonistic activity. Concerning *Hacksell et al*, Applicant argues that since the aminotetralins with N,N-dialkylation are shown to be more active than 2-N-propylamino-5-hydroxytetralin (Table I), the skilled artisan would not have been motivated to formulate compounds and compositions containing 2-N-propylamino-5-hydroxytetralin. Although *Hacksell et al* may disclose a preference for N,N-dialkylated compounds, as stated by the court in *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004), “a prior art’s mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed". While Applicants question the relevance of comparing 2-N-propylamino-5-hydroxytetralin to apomorphine (Pages 1472-1473, Table I), considering that one of ordinary skill in the art would recognize "[t]he high dopamine-receptor stimulating activity of apomorphine" (Page1469) the skilled artisan would recognize that the compounds disclosed by

Hacksell et al which are more potent than apomorphine (including 2-N-propylamino-5-hydroxytetralin) are all useable alternatives. Although Applicants further note that *Hacksell et al* disclose 18 other compounds which are more potent than apomorphine in addition to 2-N-propylamino-5-hydroxytetralin, the court, in *In re Petering*, 301 F.2d 676 (CCPA 1962) noted that a generic class encompassing 20 compounds anticipated a claim to one of those compounds. Accordingly, Applicant's argument is not found persuasive and it is maintained that the skilled artisan would have found it *prima facie* obvious to formulate compounds and compositions containing 2-N-propylamino-5-hydroxytetralin in view of *Hacksell et al*.

9. However, *Hacksell et al* do not teach the (S) enantiomer of 2-N-propylamino-5-hydroxytetralin, nor do they teach a prodrug thereof. Yet, as discussed in a previous Action, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of *Hacksell et al* with the teachings of *Wikstrom et al*. *Wikstrom et al* teach enantiomeric separation of related aminotetralins to increase dopamine agonistic activity. Specifically, *Wikstrom et al* investigated the potency of enantiomers of the structurally and functionally related compound 5-hydroxy-2-(N,N-di-n-propylamino)tetralin (5-OH-DPAT) which "have been classified as less potent in the previous studies" (Page 217, Column 1, Paragraph 3). Significantly, *Wikstrom et al* report that the (S) enantiomer of the compound, having an ED_{50} of 3.7 nmol/kg, was significantly more potent than the racemic compound (Page 219, Table III, compound 1(S)) having an ED_{50} of 11 nmol/kg (Page 219, Column 2, Paragraph 6). Accordingly, one of ordinary skill in the art at the time the invention was made would

have been motivated to subject 2-N-propylamino-5-hydroxytetralin to enantiomeric separation, and would have been especially motivated to select the (S) enantiomer of the compound.

10. Furthermore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to formulate suitable prodrugs of (S) 2-N-propylamino-5-hydroxytetralin in light of *Rodenhuis*. *Rodenhuis* teaches that hydroxylated 2-aminotetralins "display limited activity upon oral administration. A major disadvantage of the hydroxylated 2-aminotetralins and other phenolic compounds is that they undergo considerable inactivation by glucuronidation in the gut and the liver. One of the strategies to circumvent the problem of the low oral bioavailability of the hydroxylated 2-aminotetralins is to search for suitable prodrugs. Frequently investigated prodrugs of phenols are esters and carbamates" (Page 98, Chapter 6, Introduction, Paragraph 3). Thus, one of ordinary skill in the art would have been motivated to formulate prodrugs of (S) 2-N-propylamino-5-hydroxytetralin. Thus, claims 19-20 are *prima facie* obvious. Additionally, the obvious compound would necessarily be cleaved, processed or metabolized to 2-N-propylamino-5-hydroxytetralin upon administration to a human body, as recited by claim 21. Accordingly, claim 21 is also *prima facie* obvious.

11. Applicants further argue that the above rejection was based on improper hindsight reconstruction. In response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge

which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, Applicant's disclosure was not relied on as a basis for any of the rejection, but merely to indicate Applicant's acknowledgment that *Hacksell et al* do, indeed, teach racemic 2-N-propylamino-5-hydroxytetralin as having dopaminergic activity. Accordingly, Applicant's argument is not found persuasive.

12. Applicants also argue that even if motivation existed to select 2-N-propylamino-5-hydroxytetralin from *Hacksell et al* for enantiomeric separation per *Wikstrom et al* and prodrug formulation per *Rodenhuis*, predictability of outcome or reasonable expectation of success is lacking. Specifically, Applicant argues that *Wikstrom et al* teaches enhanced potency of enantiomers of N,N-dialkylated compounds. Thus, Applicant contends that the skilled artisan could not have reasonably expected the same level of success with an N-dealkylated compound. Furthermore, Applicant states that even if one of skill in the art would have expected one of the enantiomers to have a higher activity than the racemate, it could not have been predicted that specifically the (S)-enantiomer would exhibit the pronounced and functional D3 selectively of the instantly recited compounds. However, Applicant's arguments are not found persuasive. As stated by the court in *In re Deuel*, 51 F.3d 1552 (Fed Cir 1995), "[a] known compound may suggest its analogs or isomers, either geometic isomers (cis v. trans) or position isomers (e.g., ortho v. para)". While the skilled artisan may not have expected "the same level of success" using dealkylated compounds (i.e., as compared to dialkylated

compounds, as taught by *Wikstrom et al*), one of ordinary skill in the art would have still have reasonably predicted that the enantiomeric separation of the dealkylated compounds would likely provide compounds possessing advantageous properties over the racemic mixture. Furthermore, since (as discussed in a previous Action and above) *Wikstrom et al* report that the (S) enantiomer of the compound – but not the (R) enantiomer – having an ED_{50} of 3.7 nmol/kg, was significantly more potent than the racemic compound (Page 219, Table III, compound 1(S)) having an ED_{50} of 11 nmol/kg (Page 219, Column 2, Paragraph 6), one of ordinary skill in the art at the time the invention was made would have been motivated to subject 2-N-propylamino-5-hydroxytetralin to enantiomeric separation, and would have been especially motivated to select the (S) enantiomer of the compound. Although unexpected results (i.e., potentially, the pronounced and functional D3 selectivity, pure agonistic activity) may be used to overcome an obvious type rejection, the claims must be limited to the unexpected and advantageous results. In the instant case, the claims are not limited to these asserted results.

13. Accordingly, the rejection as to claims 19-21 is maintained.

14. As amended, claims 10-12 and 14 are drawn to compositions containing (S) 2-N-propylamino-5-hydroxytetralin or a prodrug thereof and a pharmaceutically acceptable carrier or adjuvant as recited by instant claim 10. As discussed above, *Hacksell et al* in view of *Wikstrom et al* and *Rodenhuis* teach (S) 2-N-propylamino-5-hydroxytetralin and prodrugs thereof. Furthermore, *Hacksell et al* specifically teach that "All substances to be tested were dissolved in saline immediately before use, occasionally with the

addition of a few drops of **glacial acetic acid**" (Page 224, Pharmacology Section, emphasis added) which encompasses compositions containing a pharmaceutically acceptable carrier or adjuvant, specifically a buffer, as recited by claim 10 as amended.

15. **Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Hacksell et al* in view of *Wikstrom et al* and *Rodenhuis* as applied to claims 10-12 and 14 above, in further view of *Jansen et al* (cited in a previous Action)**.

16. As discussed above, claims 10-12, 14 and 19-21 are taught by *Hacksell et al* in view of *Wikstrom et al* and *Rodenhuis*. However, none of the prior art teach the composition adapted for transdermal, transmucosal or parenteral administration as recited by instant claim 13.

17. As discussed in the previous Action, *Rodenhuis* teaches that hydroxylated 2-aminotetralins "display limited activity upon oral administration" and suggests formulating prodrugs to overcome this problem (Page 98, Chapter 6, Introduction, Paragraph 3). Additionally, *Jansen et al* teach "two ways to circumvent this first-pass effect… transdermal application… and oral administration of ester prodrugs" (Page 134, Column 2, Paragraph 1). Accordingly, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to adapt the compositions for transdermal delivery. Thus, claim 13 is *prima facie* obvious.

Conclusion

No new ground(s) of rejection are presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1614

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